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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
REDDIG, PETER J	
ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/775,481	WALDMAN ET AL.	
	Examiner	Art Unit	
	PETER J. REDDIG	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *February 2, 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *64, 65, 68-70, 72, 74, 75, 91-103, 132, 145, 147-148 and 150-174* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *64,65,68-70,72,74,75,91-103,132,145,147,148 and 150-174* is/are rejected.

7)☒ Claim(s) *169 and 174* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/2/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed February 2, 2009 in response to the Office Action of August 8, 2008 is acknowledged and has been entered. Claims 1-63, 66, 67,71, 73, 76-90, 104-131, 133-144, 146, and 149 have been cancelled, claims 64 and 65 have been amended, and new claims 166-174 have been added. Claims 64, 65, 68-70, 72, 74, 75, 91-103, 132, 145, 147-148 and 150-174 are currently being examined as drawn to the previously elected species of primary and metastasized colorectal cancer and 5-fluorouracil and bleomycin.

New Grounds of Rejection

Claim Objections

2. Claim 169 is objected to because of the following informalities: There is an "h" on the second line of step a), which appears to be a typographical error. Appropriate correction is required.

Claim 174 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claim, which claim 171 is. See MPEP § 608.01(n).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 174 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 174 recites the limitation "the cytostatically effective amount" in reference to claim 171. There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 64, 65, 68-70, 72, 74, 75, 91-103, 132, 145, 147-148 and 150-174 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of killing primary or metastasized colorectal cancer cells in an individual who has been identified as having primary or metastasized colorectal, said method comprising the steps in the following order: a) administering to said individual an anti-guanylyl cyclase C antibody or a guanylyl cyclase C binding fragment thereof *conjugated to a therapeutic agent*; and b) subsequently administering a different therapeutic agent, *does not* reasonably provide enablement for a method of inducing a cytostatic effect in a primary or metastasized colorectal cancer cell in an individual who has been identified as having primary or metastasized colorectal, said method comprising the step of: administering by infusion into the circulatory system of said individual, a cytostatically effective amount of an unconjugated guanylyl cyclase C ligand sufficient to have a therapeutic effect, wherein the cytostatically effective amount of an unconjugated guanylyl cyclase C ligand is an amount sufficient to maintain a concentration $\geq$EC50 of said unconjugated guanylyl cyclase C ligand for at least 15 days, wherein an unconjugated guanylyl cyclase C ligand molecules bind to guanylyl cyclase C on the surface of a primary or metastasized colorectal cancer cell in said individual and induce a cytostatic effect in said cells, a method of inhibiting the proliferation of a primary or metastasized colorectal cancer cell in an individual who has been identified as having primary or metastasized colorectal cancer, said method comprising the step of: administering into the circulatory system of said individual

a cytostatically effective amount of an unconjugated guanylyl cyclase C ligand sufficient to have a therapeutic effect, wherein the cytostatically effective amount of an unconjugated guanylyl cyclase C ligand is an amount sufficient to maintain a concentration ≥EC50 of said unconjugated guanylyl cyclase C ligand for at least 15 days, wherein an unconjugated guanylyl cyclase C ligand molecules bind to guanylyl cyclase C on the surface of a primary or metastasized colorectal cancer cell in said individual and inhibit proliferation of said cells, a method of killing primary or metastasized colorectal cancer cells in an individual who has been identified as having primary or metastasized colorectal, said method comprising the steps in the following order: a) administering to said individual a cytostatically effective amount of a guanylyl cyclase C ligand sufficient to inhibit cell proliferation by the cytostatic effect of the guanylyl cyclase C ligand, wherein guanylyl cyclase C ligand molecules bind to guanylyl cyclase C on the surface of a primary or metastasized colorectal cancer cell in said individual and inhibit proliferation of said cells and wherein the cytostatically effective amount of a guanylyl cyclase C ligand is an amount sufficient to maintain a plasma concentration ≥EC50 of said guanylyl cyclase C ligand and b) subsequently administering a different therapeutic agent, or a method of killing primary or metastasized colorectal cancer cells in an individual who has been identified as having primary or metastasized colorectal cancer, said method comprising the steps in the following order: a) administering to said individual an anti-guanylyl cyclase C antibody or a guanylyl cyclase C binding fragment thereof; and b) subsequently administering a different therapeutic agent. . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to:

64. A method of inducing a cytostatic effect in a primary or metastasized colorectal cancer cell in an individual who has been identified as having primary or metastasized colorectal, said method comprising the step of: administering by infusion into the circulatory system of said individual, a cytostatically effective amount of an unconjugated guanylyl cyclase C ligand sufficient to have a therapeutic effect, wherein the cytostatically effective amount of an unconjugated guanylyl cyclase C ligand is an amount sufficient to maintain a concentration $\geq$EC50 of said unconjugated guanylyl cyclase C ligand for at least 15 days, wherein an unconjugated guanylyl cyclase C ligand molecules bind to guanylyl cyclase C on the surface of a primary or metastasized colorectal cancer cell in said individual and induce a cytostatic effect in said cells.

65. A method of inhibiting the proliferation of a primary or metastasized colorectal cancer cell in an individual who has been identified as having primary or metastasized colorectal

cancer, said method comprising the step of: administering into the circulatory system of said individual a cytostatically effective amount of an unconjugated guanylyl cyclase C ligand sufficient to have a therapeutic effect, wherein the cytostatically effective amount of an unconjugated guanylyl cyclase C ligand is an amount sufficient to maintain a concentration ≥EC50 of said unconjugated guanylyl cyclase C ligand for at least 15 days, wherein an unconjugated guanylyl cyclase C ligand molecules bind to guanylyl cyclase C on the surface of a primary or metastasized colorectal cancer cell in said individual and inhibit proliferation of said cells.

169. A method of killing primary or metastasized colorectal cancer cells in an individual who has been identified as having primary or metastasized colorectal cancer, said method comprising the steps in the following order: a) administering to said individual a cytostatically effective amount of a guanylyl cyclase C ligand sufficient to inhibit cell proliferation h by the cytostatic effect of the guanylyl cyclase C ligand, wherein guanylyl cyclase C ligand molecules bind to guanylyl cyclase C on the surface of a primary or metastasized colorectal cancer cell in said individual and inhibit proliferation of said cells and wherein the cytostatically effective amount of a guanylyl cyclase C ligand is an amount sufficient to maintain a plasma concentration ≥EC50 of said guanylyl cyclase C ligand and b) subsequently administering a different therapeutic agent.

170. A method of killing primary or metastasized colorectal cancer cells in an individual who has been identified as having primary or metastasized colorectal cancer, said method comprising the steps in the following order: a) administering to said individual an anti-guanylyl

cyclase C antibody or a guanylyl cyclase C binding fragment thereof; and b) subsequently administering a different therapeutic agent.

The specification teaches that ligands for guanylyl cyclase C are compounds that specifically bind to the receptor and include guanylin and uroguanylin, may be a peptide or a non-peptide, and the ligands may be conjugated or unconjugated, see p. 15-lines 3-12. Thus the claims encompass using any of these ligands in an unconjugated, cytostatically effective amount sufficient to maintain a concentration ≥EC50 of said unconjugated guanylyl cyclase C ligand for at least 15 days or at least 30 days.

The specification teaches that heat-stable toxin (ST), which is a peptide produced by E. *coli,* can inhibit cell proliferation of cultured guanylyl cyclase C expressing T84 colon carcinoma cells in a CNG calcium channel dependent manner, see p. 53-59 and Figs. 1-4. The specification teaches that ST inhibited in colorectal cancer cells the release of matrix metalloproteinase 9, the organization of the actin cytoskeleton, and increased the adherence of colorectal cancer cells to type IV collagen, which are changes that could potentially inhibit the metastatic phenotype of colorectal cancer cells, see p. 63 and 64.

One cannot extrapolate the teachings of the specification to the enablement of the scope of the claims because no nexus has been established between the unconjugated ligands to guanylyl cyclase C and inducing a cytostatic effect or killing in primary or metastasized colorectal cancer cells by an amount sufficient to maintain a concentration ≥EC50 of said unconjugated guanylyl cyclase C ligand for at least 15 or at least 30 days or an amount sufficient to maintain a concentration greater than or equal to 10 time the EC50 of the GCC ligand. Furthermore, the specification has not shown what treatment protocol will maintain a

concentration ≥EC50 of said unconjugated guanylyl cyclase C ligand for at least 15 days or at least 30 days or an amount sufficient to maintain a concentration greater than or equal to 10 time the EC50 of the GCC ligand.

Shilubhai et al. (Cancer Research, Sep. 15, 2000 60:5151-5157, previously cited) teach that uroguanylin inhibits proliferation and induces apoptosis in colon adenocarcinoma cells and suppress colon polyp formation, see Abstract, Fig. 2-4 and Table 1. US Patent No. 5,879,656 teaches treating metastasized colorectal cancer with the guanylyl cyclase C ligand uroguanylin (SEQ ID NO: 5) and related GCC ligands conjugated to therapeutic agents, see the claims. However, other than uroguanylin, the art does not teach that unconjugated GCC ligands can treat primary or metastasized colorectal cancer and the development of therapeutics for malignant disorders such as colorectal cancer is well known in the art to be unpredictable.

In particular, Gura (Science, 1997, 278:1041-1042, previously cited) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Furthermore, Kaiser (Science, 2006, 313: 1370, previously cited) teaches that 90% of tumor drugs fail in patients, see 3rd col., 2nd to last para. Additionally, Young et al. (US Patent Application Pub. 2004/0180002, September 15, 2004, previously cited) teach that there have been many clinical trials of monoclonal antibodies for solid tumors. In the 1980s there were at least 4 clinical trials for human breast cancer which produced only 1 responder from at least 47 patients using antibodies against specific antigens or based on tissue selectivity. Young et al.

teach that It was not until 1998 that there was a successful clinical trial using a humanized anti-her 2 antibody in combination with cisplatin (para 0010 of the published application). The same was true in clinical trials investigating colorectal cancer with antibodies against glycoprotein and glycolipid targets, wherein the specification specifically teaches "to date there has not been an antibody that has been effective for colorectal cancer. Likewise there have been equally poor results for lung, brain, ovarian, pancreatic, prostate and stomach cancers" (para 0011 of the published application). Thus, it is clear that the art recognizes that it could not be predicted, nor would it be expected that based only on the *in vitro* data presented in the specification that it would be more likely than not that the broadly claimed un-conjugated guanylyl cyclase C ligands would predictably be useful for inducing a cytostatic effect in primary or metastasized colorectal cancer cells in an individual, inhibiting proliferation of primary or metastasized colorectal cancer cells in an individual, or to kill primary or metastasized colorectal cancer cells in an individual.

Furthermore one of skill in the art would not predictably be able to maintain a concentration $\geq$EC50 of the broadly claimed guanylyl cyclase C ligands for at least 15 days or at least 30 days or in an amount sufficient to maintain a concentration greater than or equal to 10 time the EC50 of the GCC ligand as insufficient guidance and direction has been provided as to what dose protocol would maintain a concentration $\geq$EC50 of the broadly claimed guanylyl cyclase C ligands for the indicated times at the indicated levels or that these concentrations would be effective for inducing a cytostatic effect on, inhibit proliferation of, or kill primary or metastasized colorectal cancer cell . The broadly claimed guanylyl cyclase C ligands may be degraded *in vivo* before achieving the claimed concentrations by degradation, immunological

activation or due to an inherently short half-life of the antibody. In addition, the GCC ligands may be absorbed by fluids, cells and tissues and , circulation into the target area may be insufficient to maintain the claimed concentrations of the broadly claimed guanylyl cyclase C ligands.

Given the above, in the absence of *in vivo* experimental data demonstrating a protocol would maintain a concentration ≥EC50 of the broadly claimed guanylyl cyclase C ligands for at least 15 or 30 days or maintain a concentration of greater than or equal to 10 times the EC50 of the guanylyl cyclase C ligand or that this concentration would be effective for inducing a cytostatic effect on, inhibit proliferation of, or kill primary or metastasized colorectal cancer cell, one of skill in the art could not predict that the invention will function as claimed with a reasonable expectation of success .

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and insufficient evidence has been provided which would allow one of skill in the art to predict that the invention will function as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

5. Claims 64, 65, 68-70, 72, 74, 75, 91-103, 132, 145,147-148, 150-169,171, 172 and 174 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The limitations of "wherein the cytostatically effective amount of an unconjugated guanylyl cyclase C ligand/ antibody is an amount sufficient to maintain a concentration ≥EC50 of said unconjugated guanylyl cyclase C ligand for at least 15 or at least 30 days" or "wherein the cytostatically effective amount of a guanylyl cyclase C ligand is an amount sufficient to maintain a plasma concentration ≥EC50 of said guanylyl cyclase C ligand" in claims 64, 65, 68-70, 72, 74, 75, 91-103, 132, 145,147-148, 150-169,171, 172 and 174 have no clear support in the specification and the claims as originally filed.

Applicants pointed to support for the amendments in the specification. Applicants argue that, in reference to the published Application, the specification states at ¶ 128 that the ligand can be administered at a "sufficient level" to "maintain the concentration of the ligand." to achieve a the desired effect. The specification also discusses various doses, concentrations, and time durations with respect to the level that is maintained to achieve the desired effect. For example, at ¶ 177 the specification describes an administration of a dose that is sufficient for the concentration of the ligand to "stay at or above the EC50." The specification describes maintaining the effective amount for various amounts of times, such as 20 hours. For example, at ¶ 128 the specification states that the ligand "must be present at a sufficient level for a sustained amount of time" to achieve the desired effect on the cells. Applicants argue that claims 64, 65, and 167-169 recite that a concentration is maintained for at least 15 days and/or 30 days. Support for these claims can be found where the specification describes various "Dosage Regimens" at ¶

169-171. Under the heading of "Dosage regimens" the specification describes regimens that last for at least 15 and 30 days.

A review of the suggested support reveals support for: An effective amount of ST receptor ligand must be administered to achieve inhibition of proliferation. Generally, ST receptor ligand must be present at a sufficient level for a sustained amount of time to expose cells that express ST receptors to the ST receptor ligand. Generally, enough ST receptor ligand must be administered initially and/or by continuous administration to maintain the concentration of ST ligand to be greater than about 10^{-10} M, and preferably about 10^{-9} M or more. It is preferred that such a concentration be maintained for at least about 6 hours, preferably about for at least about 8 hours, more preferably about for at least about 12 hours, in some embodiments at least 16 hours, in some embodiments at least 20 hours and up to about 24 hours or more. Regardless of whether the compound is an ST receptor ligand or ST receptor ligand conjugate which has additional functions such as cytotoxic activity or detectability, it is important that the dosage and administration be sufficient for the ST receptor binding to occur at a sufficient level for sufficient time to inhibit proliferation or to induce a therapeutic effect. Generally, the plasma concentration of ST receptor greater than about 10^{-10} M must be maintained for at least about 6 hours (para. 0128); From the above information, a bolus I.V. administration of 2.4 milligrams of ST (1.2 micromoles) as a loading dose will result in a target concentration of approximately 100 nM (10-fold higher than the EC.0), and the concentration in extracellular fluid should stay at or above the EC.50 for approximately 1.5 hours (para 177-178); Dosage Regimens: 1. Continuous infusion (infusion rate: 1 microgram/min/Kg) for a minimum of 7 days up to a maximum of 15 day, with a 7 day interval periods during which the patients undergo to a chemotherapy treatment

with a cytotoxic drug (e.g. fluorouracil, cisplatin, etc.) A mini-pump system may be employed for I.V. infusions. 2. Intermittent dosage regimens with morning (7-9 a.m.) single dose of 3.3 mg every 24 h for 30 consecutive days. This 30-day treatment can be repeated after 15-day intervals during which patients can be dosed with cytotoxic drugs (e.g. fluorouracil, cisplatin, etc.)(para. 169-171).

The suggested support is not found persuasive because there is nothing in the specification to suggest the maintaining the dose of guanylyl cyclase C ligand/ antibody in an amount sufficient to maintain a concentration ≥EC50 for at least 15 or 30 days or maintaining a plasma concentration of the guanylyl cyclase C ligand at ≥EC50 as these doses are not suggested by the cited support. . The subject matter claimed in claims 64, 65, 68-70, 72, 74, 75, 91-103, 132, 145,147-148, 150-169,171, 172 and 174 broadens the scope of the invention as originally disclosed in the specification.

Claim Rejections - 35 USC § 102

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 170-172 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent No. 5,879,656 (March, 1999, previously cited).

It is note that the broadest reasonable interpretation of claims 170-172 includes antibodies conjugated to a therapeutic agent. US Patent No. 5,879,656 teaches administering anti-guanylyl cyclase C antibodies conjugated therapeutic agents to individuals for therapy of

primary or metastasized colorectal cancer, see claims 30 -31, col. 10-lines 33-45. US Patent No. 5,879,656 teaches that individuals suffering from primary and metastasized colorectal cancer can be readily identified and the compositions of the invention can be used to kill the cancer cells, see col. 7-lines 30-65. US Patent No. 5,879,656 teaches that the pharmaceutical compositions of the present invention may be administered either as individual therapeutic agents or in combination with other therapeutic agents. The treatments of the present invention may be combined with conventional therapies, which may be administered sequentially or simultaneously, see col. 17-lines 25-33. US Patent No. 5,879,656 teaches multiple therapeutic agents such as 5-fluorouaracil and bleomycin, see the claims and col. 21-lines 35-65. Thus, given that US Patent No. 5,879,656 teaches administration of the antibodies and conventional chemotherapies, such as the described therapeutic agents, in combination sequentially or simultaneously, one of skill in the art would immediately envision administering the antibody and different therapeutic agents in the claimed order.

7. Claims 170-173 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent No. 6,767,704 (Waldman March 27, 2000).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

It is note that the broadest reasonable interpretation of claims 170-173 includes antibodies conjugated to a therapeutic agent. US Patent No. 6,767,704 teaches administering anti-guanylyl cyclase C humanized monoclonal antibodies conjugated therapeutics to individuals for therapy of primary or metastasized colorectal cancer, see claims col. 3-lines 50-55, col. 21-lines 55-60, col. 22-line 55 to col. 23-line 67, and col. 31-lines 63-67. US Patent No. 6,767,704 teaches that the compositions of the invention can be used to kill the cancer cells, see col. 21-lines 45-55. US Patent No. 6,767,704 teaches that the pharmaceutical compositions of the present invention may be administered either as individual therapeutic agents or in combination with other therapeutic agents. The treatments of the present invention may be combined with conventional therapies, which may be administered sequentially or simultaneously, see col. 26-lines 4-11. US Patent No. 6,767,704 teaches multiple therapeutic agents such as 5-fluorouaracil and bleomycin, see col. 22-line 55 to col. 23-line 67. Thus, given that US Patent No. 6,767,704 teaches administration of the antibodies and conventional chemotherapies, such as the described therapeutic agents, in combination sequentially or simultaneously, one of skill in the art would immediately envision administering the antibody and different therapeutic agents in the claimed order.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claim 173 is rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,879,656 (March, 1999, previously cited) as applied to claims 170-172 above, in further view of Queen *et al.* (Proc. Natl. Acad. Sci. 1989, Vol. 86, pages 10029-10033, previously cited), and in further view of Riechmann et al (Nature Vol 332:323-327 1988, previously cited).

US Patent No. 5,879,656 teaches as set forth above, but does not teach humanized anti-guanylyl cyclase C monoclonal antibody.

Queen et al teach a reproducible technique for making humanized monoclonal antibodies (page 11030, col. 2 para 3) and further teaches that for human applications humanized

monoclonal antibodies are more useful because of their reduced immunogenicity (page 10029, col. 2).

Riechmann et al teach the "reshaping of human antibodies for therapy" (see Title) in which a "human IgG1 antibody has been reshaped for serotherapy in humans by introducing the six hypervariable regions from the heavy- and light-chain domains of a rat (monoclonal) antibody directed against human lymphocytes" (see Abstract). Thus, Riechmann et al fully disclose how one skilled in the art would use recombinant DNA techniques to sequence, clone and humanize a monoclonal antibody, with a reasonable expectation of success. Further, Riechmann et al provide one skilled in the art with the motivation to humanize the antibodies for use as human pharmaceutical. Riechmann et al teach, "the foreign immunoglobulin can elicit an anti-globulin response which may interfere with therapy or cause complex hypersensitivity." (page 323, column 1, first full paragraph). Humanized "chimeric antibodies have at least two advantages over mouse antibodies. First, the effector functions can be selected or tailored as desired. Second, the use of human rather than mouse isotypes should minimize the anti-globulin responses during therapy by avoiding anti-isotypic antibodies" (see page 323, bridging paragraph, columns 1-2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to and one of ordinary skill in the art would have been motivated to make and use humanized monoclonal forms of the anti-GCC antibodies of 5,879,656 with a reasonable expectation of success because Queen *et al.* teach the advantage of using humanized monoclonal antibodies to reduce immunogenicity. In addition, Riechmann et al have demonstrated the successful genetically engineering and humanization of rat and mouse

monoclonal antibodies, which are also useful for reducing the anti-globulin responses during therapy by avoiding anti-isotypic antibodies.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 170-173 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 30-32, 35-38, 40-55, and 57-65 of copending Application No. 10/866,951 in view of Cohen (Int J Radiat Oncol Biol Phys, 1987, 13:251-8, previously cited), in further view of Queen *et al.* (Proc. Natl. Acad. Sci. 1989, Vol. 86, pages 10029-10033, previously cited), and in further view of Riechmann et al (Nature Vol 332:323-327 1988, previously cited).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application and the instant application are claiming common

subject matter. The claims of both the copending application and the instant application are drawn to a method of treating an individual with esophageal cancer comprising administering a GCC ligand and active agent, wherein the ligand is an antibody or monoclonal antibody and is conjugated to the agent, wherein the agent is a chemotherapeutic, toxin, or radiosensitizing agent, wherein the agent inhibits cell division, wherein the agent is bleomycin or 5-FU,.

Cohen teaches that to find the safest procedure for treating a tumor, one must search for that combination of factors which will maximize the conditional probability of controlling the tumor and avoiding injury in any normal tissues, this depends on several factors including dose, field-size, fractions, and time (abstract).

Queen et al teach a reproducible technique for making humanized monoclonal antibodies (page 11030, col. 2 para 3) and further teaches that for human applications humanized monoclonal antibodies are more useful because of their reduced immunogenicity (page 10029, col 2, para 2).

Riechmann et al teach the "reshaping of human antibodies for therapy" (see Title) in which a "human IgG1 antibody has been reshaped for serotherapy in humans by introducing the six hypervariable regions from the heavy- and light-chain domains of a rat (monoclonal) antibody directed against human lymphocytes" (see Abstract). Thus, Riechmann et al fully disclose how one skilled in the art would use recombinant DNA techniques to sequence, clone and humanize a monoclonal antibody, with a reasonable expectation of success. Further, Riechmann et al provide one skilled in the art with the motivation to humanize the antibodies for use as human pharmaceutical. Riechmann et al teach, "the foreign immunoglobulin can elicit an anti-globulin response which may interfere with therapy or cause complex hypersensitivity."

(page 323, column 1, first full paragraph). Humanized "chimeric antibodies have at least two advantages over mouse antibodies. First, the effector functions can be selected or tailored as desired. Second, the use of human rather than mouse isotypes should minimize the anti-globulin responses during therapy by avoiding anti-isotypic antibodies" (see page 323, bridging paragraph, columns 1-2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use different times of administration of the conjugated GCC antibody or therapeutic agents taught by 10/866,951, because Cohen teaches the best tumor treatment scheme is to maximize the chance of tumor control by optimizing factors such as dose and number of fractions and avoid complications. One would have been motivated to use different times of administration and combinations of conjugated guanylyl cyclase C antibody and therapeutic agents in order to optimize the treatment of the colorectal cancer and to avoid complications such as injury to normal tissue.

Additionally, one of ordinary skill in the art would have been motivated to make and use humanized forms of the monoclonal antibodies of 10/866,951with a reasonable expectation of success because Queen *et al.* teach the advantage of using humanized antibodies to reduce immunogenicity. In addition, Riechmann et al have demonstrated the successful genetically engineering and humanization of rat and mouse antibodies, which are also useful for reducing the anti-globulin responses during therapy by avoiding anti-isotypic antibodies.

This is a provisional obviousness-type double patenting rejection.

Applicants argue that non-statutory obviousness-type double patenting rejections are based on allowed claims. Applicants argue that neither the instant Application nor the '951 have allowed claims so the double patenting rejection is proper.

Applicants' arguments have been considered, but have not been found persuasive because a provisional double patenting rejection is proper between two pending applications, see MPEP 804, charts IA & IB.

10. Claims 170-173 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 5, 7, 9, 10, 15-18, 23, 28-35, 38-43 46-50, and 53-58 of US Patent 5,879,656, (March, 1999, previously cited), in view of Cohen (Int J Radiat Oncol Biol Phys, 1987, 13:251-8 , previously cited), in further view of Queen *et al.* (Proc. Natl. Acad. Sci. 1989, Vol. 86, pages 10029-10033, previously cited), and in further view of Riechmann et al (Nature Vol 332:323-327 1988, previously cited).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the Patent and the instant application are claiming common subject matter. The claims of both the copending application and the instant application are drawn to a method of treating an individual with metastasized colorectal cancer comprising administering guanylyl cyclase C (ST receptor) binding moiety and active moiety, wherein the binding moiety is an antibody or binding fragment thereof and is conjugated to the active moiety, wherein the active moiety is a chemotherapeutic, toxin, or radiosensitizing agent, bleomycin or 5-FU.

Cohen teaches as set forth above.

Queen et al teach as set forth above.

Riechmann et al teach as set forth above.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use different times of administration of the conjugated GCC antibody or therapeutic agents taught by US Patent 5,879,656, because Cohen teaches the best tumor treatment scheme is to maximize the chance of tumor control by optimizing factors such as dose and number of fractions and avoid complications. One would have been motivated to use different times of administration and combinations of conjugated guanylyl cyclase C antibody and therapeutic agents in order to optimize the treatment of the colorectal cancer and to avoid complications such as injury to normal tissue.

Additionally, one of ordinary skill in the art would have been motivated to make and use humanized monoclonal forms of the anti-GCC antibodies of 5,879,656 with a reasonable expectation of success because Queen *et al.* teach the advantage of using humanized antibodies to reduce immunogenicity. In addition, Riechmann et al have demonstrated the successful genetically engineering and humanization of rat and mouse antibodies, which are also useful for reducing the anti-globulin responses during therapy by avoiding anti-isotypic antibodies.

11. Claims 170-173 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6-8 of US Patent 6,060,037 in view of US Patent 5,879,656, (March 1999, previously cited), in view of Cohen (Int J Radiat Oncol Biol Phys, 1987, 13:251-8 , previously cited), in further view of Queen *et al.* (Proc. Natl. Acad. Sci. 1989, Vol. 86, pages 10029-10033, previously cited), and in further view of Riechmann et al (Nature Vol 332:323-327 1988, previously cited).

Claims 6-8 of US Patent 6,060,037 are drawn to a method of treating an individual suspected of suffering from metastasized colorectal cancer comprising the step of administering parenterally to said individual a therapeutically effective amount of a sterile pharmaceutical composition that comprises a) a pharmaceutically acceptable carrier or diluent, and, b) a conjugated compound which comprises i) a ST receptor binding moiety; and, ii) an active moiety that is a therapeutic agent that causes cell death; wherein said conjugated compound binds to an ST receptor on a metastasized colorectal tumor cell and said active moiety causes the death of said cell and, wherein said pharmaceutical composition is administered for delivery into said individuals circulatory system.. A method of treating an individual suspected of suffering from metastasized colorectal cancer comprising the step of administering parenterally to said individual for delivery into said individual's circulatory system a therapeutically effective amount of a pharmaceutical composition comprising: a) a pharmaceutically acceptable carrier or diluent, and, b) an amount of conjugated compound effective for therapeutic use in a human suffering from colorectal cancer, said conjugated compound comprising: i) an ST receptor binding moiety; and, ii) an active moiety; wherein said pharmaceutical composition is sterile and said active moiety is a radioactive agent; wherein said conjugated compound binds to ST receptors on a metastasized colorectal cancer cell and accumulates on said cell, and radiation emitted from accumulated conjugated compound on said cell causes the death of said cell.

US Patent 6,060,037 contemplates antibodies as a receptor binding moiety, see col. 11, lines 1-7.

US Patent 5,879,656 teaches as set forth above.

Cohen teaches as set forth above.

Queen et al teach as set forth above.

Riechmann et al teach as set forth above.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use different times of administration of the conjugated GCC antibody or therapeutic agents taught by US Patents 6,060,037 and 5,879,656, because Cohen teaches the best tumor treatment scheme is to maximize the chance of tumor control by optimizing factors such as dose and number of fractions and avoid complications. One would have been motivated to use different times of administration and combinations of conjugated guanylyl cyclase C antibody and therapeutic agents in order to optimize the treatment of the colorectal cancer and to avoid complications such as injury to normal tissue.

Additionally, one of ordinary skill in the art would have been motivated to make and use humanized monoclonal forms of the anti-GCC antibodies of 6,060,037 with a reasonable expectation of success because Queen *et al.* teach the advantage of using humanized antibodies to reduce immunogenicity. In addition, Riechmann et al have demonstrated the successful genetically engineering and humanization of rat and mouse antibodies, which are also useful for reducing the anti-globulin responses during therapy by avoiding anti-isotypic antibodies.

12. Claims 170-173 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 14-16 US Patent 6,087,109 (July, 2000), in view of US Patent 5,879,656, (March 1999, previously cited), in view of Cohen (Int J Radiat Oncol Biol Phys, 1987, 13:251-8 , previously cited), in further view of Queen *et al.*

(Proc. Natl. Acad. Sci. 1989, Vol. 86, pages 10029-10033, previously cited), and in further view of Riechmann et al (Nature Vol 332:323-327 1988, previously cited).

Claims 14-16 of US Patent 6,087,109 are drawn to a method of treating an individual suspected of suffering from colorectal cancer comprising the steps of administering to said individual a therapeutically effective amount of a pharmaceutical composition comprising a conjugated compound comprising: a) a ST receptor binding moiety; and, b) an active moiety; wherein said active moiety is an antisense molecule, wherein said pharmaceutical composition is administered orally, or wherein said pharmaceutical composition is administered intravenously.

US Patent 6,087,109 contemplates antibodies as a receptor binding moiety, see col. 9, lines 25-33.

US Patent 5,879,656 teaches as set forth above.

Cohen teaches as set forth above.

Queen et al teach as set forth above.

Riechmann et al teach as set forth above.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use different times of administration of the conjugated GCC antibody or therapeutic agents taught by US Patents 6,087,109 and 5,879,656, because Cohen teaches the best tumor treatment scheme is to maximize the chance of tumor control by optimizing factors such as dose and number of fractions and avoid complications. One would have been motivated to use different times of administration and combinations of conjugated guanylyl cyclase C antibody and therapeutic agents in order to optimize the treatment of the colorectal cancer and to avoid complications such as injury to normal tissue.

Additionally, one of ordinary skill in the art would have been motivated to make and use humanized monoclonal forms of the anti-GCC antibodies of 6,087,109 with a reasonable expectation of success because Queen *et al.* teach the advantage of using humanized antibodies to reduce immunogenicity. In addition, Riechmann et al have demonstrated the successful genetically engineering and humanization of rat and mouse antibodies, which are also useful for reducing the anti-globulin responses during therapy by avoiding anti-isotypic antibodies.

13. All other objections and rejections recited in August 8, 2008 are withdrawn.

14. No claims allowed.

15. This action is a **final rejection** and is intended to close the prosecution of this application. Applicant's reply under 37 CFR 1.113 to this action is limited either to an appeal to the Board of Patent Appeals and Interferences or to an amendment complying with the requirements set forth below.

If applicant should desire to appeal any rejection made by the examiner, a Notice of Appeal must be filed within the period for reply identifying the rejected claim or claims appealed. The Notice of Appeal must be accompanied by the required appeal fee.

If applicant should desire to file an amendment, entry of a proposed amendment after final rejection cannot be made as a matter of right unless it merely cancels claims or complies with a formal requirement made earlier. Amendments touching the merits of the application which otherwise might not be proper may be admitted upon a showing a good and sufficient reasons why they are necessary and why they were not presented earlier.

A reply under 37 CFR 1.113 to a final rejection must include the appeal form, or cancellation of, each rejected claim. The filing of an amendment after final rejection, whether or not it is entered, does not stop the running of the statutory period for reply to the final rejection unless the examiner holds the claims to be in condition for allowance. Accordingly, if a Notice of Appeal has not been filed properly within the period for reply, or any extension of this period obtained under either 37 CFR 1.136(a) or (b), the application will become abandoned.

16 Applicant's amendment necessitated the new grounds of rejection. Thus, **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Peter J. Reddig
Examiner
Art Unit 1642

/Karen A Canella/

Primary Examiner, Art Unit 1643